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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,824	12/10/2001	Philippe Collas	50195/002002	7491

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/015,824	COLLAS ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14-16,18-23 and 32-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14-16,18-23 and 32-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 12/15/03, been entered. Claims 1, 2, 14-16, 18, 20-23 have been amended. Claims 32-49 have been added. Claims 1, 2, 14-16, 18-23, 32-49 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2, 14-16, 18-23 and newly added claims 32-41 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is *maintained* for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that in order to practice the claimed invention, one of skill in the art would not need to know what factors would be added or removed during incubation of a cell nucleus or chromatin mass. Applicants argue that what is important is that a factor be added or removed during incubation. Applicants argue that the significance of the recitation of the addition or removal of a factor from the incubated nucleus or chromatin mass is to define conditions under which the

nucleus or chromatin mass is incubated; if the conditions do not permit addition or removal of a factor, then the method would not be covered by the claim. Applicants argue that one in art would not require knowledge of the factors to be added or removed in order to ascertain whether suitable conditions are present, because the identity of any added or removed factor is not "essential or critical". See p. 10, last ¶ of Applicants' Response.

Applicants' arguments are not persuasive. The claims as amended, as to methods of altering gene expression by incubation of a nucleus from a donor cell with a reprogramming media under conditions that allow for the removal or addition of a factor from said nucleus and then the insertion of the nucleus or chromatin mass formed by said nucleus into a recipient somatic cell or cytoplast. The specification fails to provide adequate written description for what factors would be removed or added from the nucleus in order to alter gene expression. Although the specification broadly contemplates factors that may be included in a reprogramming media, and defines "removal of a factor" as the dissociation of a factor from chromatin, a chromosome, or a component of the nuclear envelope [see p. 18, lines 17-22], the specification fails to describe with particularity, the addition or removal of factor, which when used in the claimed methods would produce a cell with altered gene expression, to indicate that Applicants had possession of the claimed invention. As the specification teaches that the cell with "altered gene expression" would be of a "desired cell type" [see p. 21, lines 12-13, for example], one

of skill in the art would need to know the factor(s) to be added or removed in order to direct the reprogramming of the original cell into a desired cell type. The Examiner contends that the factors to be removed or added from the nucleus would be essential and critical to the invention because without knowing what factor(s) would be removed or added from a nucleus, one of skill in the art could not envision what factors, when used as claimed, would result in a cell with altered gene expression of a particular cell type.

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, as no factors, which would be removed or added into the donor nucleus to form a reprogrammed cell, were described, they do meet the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2, 14-16, 18-23 and newly added claims 32-49 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is *maintained* for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amended claims are directed to methods of altering gene expression in a cell. Applicants argue that the instant application is replete with examples, where the exposure of a donor cell nucleus with a reprogramming media, gene expression is significantly altered but endogenous gene expression of the donor nucleus is not entirely eliminated. Applicants argue that such altered gene expression is a reprogramming, where the gene expression of "reprogrammed" cell is different from

that of a cell not exposed to the reprogramming media. See p. 11 of Applicants' Response.

Applicants' arguments are not persuasive. The specification teaches that the methods of reprogramming may be used to convert a cell type into another cell type that is closely related by origin or character, or that a cell may be converted into a desired cell type that is distantly related to the donor cell and thus shares few or no characteristics or functions with donor cell. See p. 30, lines 1-8. The specification teaches that the reprogrammed cells of the invention would be used to treat or prevent diseases or disorders. See pp. 6-8 of the specification. The claims are not enabling because the instant specification fails to provide teachings, guidance or evidence with regard to the reprogramming or alteration of gene expression of the resulting cells, such that one of skill in the art could predictably produce cells of any desired cell type for treatment of any disease, as broadly contemplated.

Although the specification provides teachings to show that exposure of nuclei to extracts would increase expression in various genes, the specification fails to teach or provide guidance to show that the removal or addition of a specific factor would specifically result in cells that would have altered gene expression of any desired cell type, as broadly contemplated. Furthermore, as the claims as broadly written, encompass methods of reprogramming of the donor cell, the specification fails to provide teachings to show that the cells produced by the claimed methods are reprogrammed. The amendments to the claims, which recite "altered gene

expression" encompass cells that are partially or fully reprogrammed. The specification fails to enable the instant invention because the specification fails to teach or provide guidance for the starting materials, for example, factors present in the reprogramming extract that would be used to practice the claimed methods.

Applicants argue that because the claims have been amended to specify that the recipient cell is a somatic cell, and that the references relied upon by the Office in the prior Office action supporting the position that reprogramming [*i.e.*, cloning] is unpredictable are not relevant to the pending claims because they summarize the use of reprogramming in the field of cloning, which is an entirely different endeavor from the instant application. Applicants argue that because in the field of cloning, an entire cloned animal would require complete reprogramming, whereas the claimed reprogramming method of the present application does not include the use of oocytes, because the claims require that the recipient cell be a somatic cell, and production of a cell that is not fully converted is nonetheless useful. See pp. 11-12, bridging ¶ of Applicants' Response.

This is not found to be persuasive. The claims as amended encompass methods of nuclear transfer because the claims recite that a nucleus that has been incubated in a reprogramming media would then be inserted into a recipient somatic cell or cytoplast. An enucleated oocyte, as those used in nuclear transfer methods, would be considered a cytoplast. The specification supports this by defining a cytoplast as a membrane enclosed cytoplasm, which may be derived, for

example, from nucleated or enucleated cells. See p. 17, lines 1-8. Accordingly, the art cited in the prior Office action is germane to the instant invention because the claims encompass nuclear transfer and the reprogramming of a donor cell. The recitation of "altering gene expression" encompasses an increase, a decrease, a partial or complete alteration of gene expression. Thus, somatic cell nuclear transfer, wherein a donor cell is completely reprogrammed [such as the case of cloning] is encompassed by the claim. As such, in light of the state of the art of reprogramming, the specification fails to provide teachings or guidance to show that the cells of the invention are indeed reprogrammed. The mere showing of gene expression is not sufficient evidence to show that the cells produced by the claimed method are reprogrammed, as methods well known in the art can change gene expression. For example, introduction of cells to cytokines can turn on gene expression.

As such, in view of the specification's lack of teaching or guidance with regard to factors that are either removed from the donor nucleus, or addition of factors from the reprogramming media, the lack of teaching or guidance to show that the cells resulting from the claimed method would be reprogrammed or could be directed to have an altered gene expression of a particular cell type, the unpredictable and undeveloped state of the art with regard to reprogramming, it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejections of claims 4-9 and 31 under 35 U.S.C. 102(b) are rendered moot in view of Applicants' cancellation of the claims.

Claims 1, 21, 22 and newly added claims 36 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by DiBerardino *et al.* [**PNAS**, 83:8231-8234, Nov. 1986].

Applicants argue that the transfer of a nucleus from one cell into a recipient somatic cell is neither taught nor suggested by DiBerardino, and thus, the prior rejection should be withdrawn. See p. 13 of Applicants' response.

This is not found to be persuasive. The claims as amended recite that the recipient cell can be a somatic cell or a cytoplast. The specification defines a cytoplast as a membrane-enclosed cytoplasm, which can be formed from nucleated or enucleated cells, and thus encompasses intact cells. See p. 14, lines 1-8 of the specification. Thus, the enucleated oocytes, as taught by DiBerardino, anticipate the "cytoplast" as required by the claims.

DiBerardino teach the generation of feeding tadpoles that were cloned from *Rana* erythrocyte nuclei. Particularly, they teach that the membranes of donor erythrocytes were broken down by osmotic rupture and the contents of 1-10 cells were injected into oocytes. Approximately 24 hours after the oocytes completed maturation, they were activated parthenogenetically, and the nuclear transplants were observed through at least the first three cleavage stages. The resulting cells were used as donor cells in a nuclear transplantation method. See *Materials & Methods.*

Note that the specification broadly defines a reprogramming media as any media that allows the removal or a factor from a nucleus, chromatin mass, or chromosome, or the addition of a factor from the solution from the solution to the nucleus, chromatin mass, or chromosome. See p. 17, lines 11-13 of the specification. As such, the incubation of frog erythrocyte nuclei into enucleated oocytes would fulfill the limitations of the claim invention, as the generation of feeding tadpoles would show an altered gene expression of the erythrocyte nuclei, as required by the claims.. Accordingly, DiBerardino anticipate the claimed invention.

Claims 1, 21-23 and newly added claims 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Schnieke *et al.* for reasons of record.

Applicants argue that the transfer of a nucleus from one cell into a recipient somatic cell is neither taught nor suggested by Schnieke, and thus, the prior rejection should be withdrawn. See p. 13 of Applicants' response.

This is not found to be persuasive. The claims as amended recite that the recipient cell can be a somatic cell or a cytoplast. The specification defines a cytoplast as a membrane-enclosed cytoplasm, which can be formed from nucleated or enucleated cells, and thus encompasses intact cells. See p. 14, lines 1-8 of the specification. Accordingly, an enucleated oocyte, as taught by Schnieke, anticipates the recitation of a "cytoplast" and the prior rejection is maintained.

Schnieke teach the generation of transgenic sheep produced by the transfer of fetal fibroblast nuclei into enucleated oocytes. Particularly they teach that Poll Dorset fetal fibroblasts [PDFF2] were transfected and cultured. The cell nuclei were then transferred into enucleated oocytes. See p. 2131, col. 2-3. Note that Schnieke teaches the claimed invention because the claimed mechanism is not defined by the specification; in particular, the factors that are removed or added are not specifically defined by the specification. Furthermore, the generation of a live born sheep would show that the fetal fibroblasts have an altered gene expression, as required by the claims. Accordingly, Schnieke anticipate the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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